REMARKS:

Claims 1 and 16 have been amended to state that the animal is undergoing a dysregulated inflammatory response or a life threatening immunological reaction, that is, SIRS or sepsis. Support for these amendments may be found at least at paragraph 0003 and paragraph 0006 of the instant application.

Claims 17-20 have been added which correspond to claims 2-5 but depend on claim 16 rather than on claim 1.

As discussed in Published US Patent Application 2004/0214792 (the instant application), 'sepsis is characterized by an overwhelming systemic response to infection and may lead to septic shock. Septic shock is a life threatening immunological reaction to a severe infection' (paragraph 0003). As discussed in this application, a filterable cardiodepressant substance (FCS) was previously detected in animals undergoing sepsis (paragraph 0009). As discussed in paragraph 0011, the inventors made the surprising discovery that this filterable cardiodepressant substance was lysozyme c. As discussed below, the inventors were further able to demonstrate that inhibitors of lysozyme c can inhibit, prevent or reduce myocardial dysfunction in an animal undergoing sepsis.

Specifically, as discussed in the instant application, lysozyme c from disintegrating leukocytes caused by the 'over-active' immune response contribute to myocardial dysfunction by binding to or hydrolyzing cardiac membrane glycoproteins, thereby interfering with myocardial excitation coupling (paragraph 0058). Accordingly, any substance that would inhibit the binding of lysozyme or reduce the quantity of lysozyme available for binding or reduce the total quantity of lysozyme would be beneficial as a treatment for sepsis or SIRS in that these agents would reduce lysozyme's ability to interfere with myocardial excitation coupling..

Thus, the inventors have shown that lysozyme c contributes to the myocardial dysfunction observed in septic shock. This relationship could not have been predicted and it

was previously believed that there was no link between lysozyme and myocardial dysfunction in an inflammatory process such as sepsis.

Claims 1-16 were rejected under 35 USC 112 for lacking enablement. Specifically, the office action states that 'the specification, while being enabling for the treatment of myocardial dysfunction and an inflammatory response, does not reasonably provide enablement for a method of preventing or reducing the myocardial dysfunction and an inflammatory response ... and while being enabling for inhibitory effects of N,N' diacetylchitobiose as an inhibitor of lysozyme, does not reasonably provide enablement for any agent that can inhibit lysozyme to a cell or animal in need thereof'.

As discussed above, claim 1 has been amended so as to be directed to preventing or reducing myocardial dysfunction in an animal undergoing a dysregulated inflammatory response (for example SIRS) or a life threatening immunological reaction (for example sepsis). Claim 13 is directed to a method of preventing or reducing the onset of myocardial dysfunction in an animal with sepsis. Claim 14 is directed to a method of reversing myocardial depression in an animal with sepsis. Claim 16 is directed to a method of treating sepsis or SIRS.

Regarding preventing, reducing or reversing myocardial dysfunction in an animal undergoing for example sepsis or SIRS, as discussed in paragraphs 0175 and 0176 of the instant application, the inventors carried out a late treatment study to see if an inhibitor of lysozyme (TAC) would reverse myocardial depression and an early treatment study to determine the effect of administering a lysozyme inhibitor during sepsis but before myocardial depression developed. As discussed at paragraph 0196, 'the results showed that TAC prevented the reduction in stroke-work as compared with the nontreated sepsis group'. Regarding the late treatment study, it was noted that 'although there appeared to be limited response to treatment in some experiments, this increase was relatively small and SW [stroke-work] remained quite reduced as compared with the pre-sepsis measurement.'

(paragraph 0196). However, at paragraph 0198, it is stated that 'In LTS, the dose of TAC may have been too small to reverse myocardial depression and therefore a higher dose of treatment may have been able to competitively remove Lzm-S from the cardiac membrane. Alternatively, hydrolysis of the membrane glycoprotein by Lzm-S may have irreversibly injured the muscle making it unsusceptible to inhibition by TAC'.

Regarding agents that inhibit lysozyme, it is noted that these are well known in the art and are discussed in detail at least at paragraphs 0074-0111 of the instant application. It is noted that the inventors did not discover lysozyme or lysozyme inhibitors but rather discovered that lysozyme is the filterable cardiodepressant substance causing myocardial depression in animals undergoing a dysregulated immune response or a life-threatening immunological reaction.

Furthermore, as discussed at least at paragraph 0118 of the instant application, 'the mechanism may relate to its [lysozyme c] binding or hydrolysis of a cardiac membrane glycoprotein thereby interfering with myocardial excitation contraction coupling in sepsis'. Accordingly, anything that will reduce the binding of lysozyme to the heart reverses or treats myocardial depression caused by lysozyme. That is, any substance that would inhibit the binding of lysozyme or reduce the quantity of lysozyme available for binding or reduce the total quantity of lysozyme would be beneficial. As discussed above, such agents are well known in the art and examples of such agents are provided at least at paragraphs 0074-0111 of the instant application.

Accordingly, it is held that the applicant has demonstrated that known lysozyme inhibitors or known methods of reducing lysozyme can be used to treat sepsis or SIRS and can be used to prevent or reduce myocardial depression during an immunological reaction such as SIRS or sepsis, as discussed above.

Accordingly, it is held that factors (1) – (8) of Wands have been met as inhibitors of lysozyme are well known in the art and are described at paragraphs 0074-0111 of

the instant application and the amount of experimentation would therefore be well within the skill of one knowledgeable of the art. Furthermore, preventing and reducing myocardial dysfunction has been taught by the early treatment study as discussed above which teaches that administering a lysozyme inhibitor to an animal undergoing sepsis or SIRS prior to onset of myocardial dysfunction will prevent or reduce myocardial dysfunction. It is further noted that as discussed above, the mechanism of action is also described and accordingly any substance that would inhibit the binding of lysozyme or reduce the quantity of lysozyme available for binding or reduce the total quantity of lysozyme would be beneficial as a treatment for sepsis or SIRS.

It is respectfully requested that the examiner reconsider this objection in view of the above arguments and the amendments to the claims.

Claims 1-16 were rejected under 35 USC 103(a) as obvious over Valisena et al., 1996, Microbiologica 19: 25-30 (Valisena) in combination with Rand-Meir et al., 1969, Biochemistry 8: 4206-4214 (Rand-Meir) and Rubio et al., 1973, Immunochemistry 10: 361-364 (Rubio).

Specifically, the office action states that 'Valisena teaches that a substance that can inhibit lysozyme should also interfere in the regulation of cell differentiation and the regulation of immune response, which are the major roles of lysozyme ... Valisena is silent in disclosing specifically the treatment of the myocardial dysfunction and an inflammatory response by inhibiting the lysozyme with said agent however it is the inherent property of an agent having at least two N-acetylglucosamine units to inhibit lysozyme thus effective in the treatment of the myocardial dysfunction and an inflammatory response.'

The office action further states that Rand-Meir 'teaches that lysozyme binds chitin oligosaccharides to a series of subsites, three of which form a strong enzyme-inhibitor complex with chitotriose'.

The office action further states that Rubio 'teaches the effect of lysozyme inhibitor N-acetyl-D-glucosamine (NAG) unable to avoid precipitation of the enzyme by its antibodies. Rubio discloses the inhibitory effects of NAG and antibodies on lysozyme wherein the antibody does not displace NAG from the complex of the enzyme-inhibitor. Furthermore, Rubio discloses that an antibody can prevent NAG from reaching subsite C of lysozyme and conversely, NAG prevents antibody from neutralizing lysozyme.'

Regarding Valisena, it is noted that as discussed in the discussion section on page 28, this reference teaches that 'HEWL inhibitors such as histidine methylester, heparin, chitotriose and chitobiose all have an immune-enhancing effect...' (emphasis added). The reference further states that the authors had previously shown that 'lysozyme of different origin can modulate the *in vitro* response of immune cells to mitogens, depress the primary immune response to SRBC and BSA in mice and strongly reduce the immuno effect of some known adjuvants' (emphasis added). Valisena further teaches that 'the mechanism whereby adjuvants stimulate immune response might be dependent on their ability to inhibit endogenous lysozyme, thus abolishing the immunosuppressive effect of this enzyme' (emphasis added, top of page 29).

Thus, Valisena teaches that lysozyme inhibits an immune response and that inhibitors of lysozyme should be used as adjuvants in order to increase or enhance an immune response. Extending these teachings to the treatment of disorders such as sepsis or SIRS wherein the immune system is 'over-active' in response either to a severe infection or has otherwise become dysregulated, one would therefore predict that treatment of these individuals with an effective amount of lysozyme would have a beneficial effect, as one would predict, based on Valisena, that the lysozyme would an immunosuppressive effect. Accordingly, based on Valisena, one would predict that administering lysozyme to an individual undergoing sepsis or SIRS would have beneficial effects in that it would reduce the level of the immune response while administering a lysozyme inhibitor would have the

opposite effect, that is, that the lysozyme inhibitor would increase the immune response, thereby worsening the symptoms. As the examiner will appreciate, the inventors have discovered that completely the opposite occurs – additional lysozyme would bind to the heart, thereby increasing myocardial depression with disastrous consequences while treatment with a lysozyme inhibitor as discussed above reduces or prevents myocardial depression. Accordingly, it is held that the inventors' invention is clearly distinguished from and is fact taught against by Valisena.

Further and more favorable consideration is respectfully requested.

Respectfully submitted

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